PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/48	A1	(11) International Publication Number: WO 00/27367 (43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/GB99/03649

(22) International Filing Date: 4 November 1999 (04.11.99)

(30) Priority Data:
9824658.0 11 November 1998 (11.11.98) GB
9925166.2 25 October 1999 (25.10.99) GB

(71) Applicant *(for all designated States except US)*: BIO-PROGRESS TECHNOLOGY INTERNATIONAL INCORPORATED [US/US]; P.O. Box 500127, Atlanta, GA 31150 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BROWN, Malcolm, David [GB/GB]; 87 The Lammas, Mundford, Norfolk IP26 5DS (GB). MUNCASTER, Barry, John [GB/GB]; 8 Burling Walk, Milton, Cambridgeshire CB4 6DX (GB). NOWAK, Edward, Zbygniew [GB/GB]; 4 Davey Close, Impington, Cambridge CB4 9YJ (GB).

(74) Common Representative: KEITH W NASH & CO; Chartered Patent Agents & European Patent Attorney, s, 90–92 Regent Street, Canbridge CB2 1DP (GB).

(81) Designated States: AU, CA, CZ, IL, IN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: A CAPSULE BASED DRUG DELIVERY SYSTEM

(57) Abstract

A soft capsule made from animal free materials using coatings to achieve superior bonding and variable release characteristics. Also disclosed is an encapsulating apparatus by which the capsules may be produced.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	R	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Title: A capsule based drug delivery system

Field of Invention

This invention concerns the production of drug delivery systems and relates to soft capsule forming materials and encapsulation apparatus for these materials.

Background to the Invention

The provision of soft capsules containing pharmaceutical preparations is well established. Typically drugs and dietary supplements are encapsulated in soft or hard gelatin shells designed to release their contents under specific conditions encountered in the body. The gelatin shells used for these capsules are derived from animal renderings.

With concerns of animal related diseases such as Bovine Spongiform Encephalopathy (BSE), and the existence of large groups of the population unable or unwilling to take animal based products for religious or ethical reasons, there is a profound need for a substitute material for soft capsule shells. However the machinery used in the production of gelatin capsules does not lend itself to the use of alternative materials, particularly those suitable for ingestion. In addition those materials which perform in a similar fashion mechanically to gelatin do not have suitable barrier properties to prevent spoilage of certain sensitive ingredients. As a result it is necessary to change not only the capsule material, but also the machinery used for their production. It is this change in material and the necessary processing means which this invention addresses, by providing the means to produce sealed, ingestible capsules with good barrier properties and optional controlled release.

Summary of the Invention

The present invention provides encapsulating films having robust mechanical properties and good oxygen barrier when used as a capsule wall. The films created are preferably but not essentially coated to achieve precise drug delivery and protection of their contents and use a carrier membrane which also acts as the sealing layer. The sealing layer is typically a modified cellulose 18 to 200 microns thick and soluble in cold water. The coatings control the time and site of release of the finished capsules as well as offering specific barrier properties to prevent the spoilage of the capsule contents. The conversion process involves film transport, coating, vacuum forming, filling, sealing and cutting.

The materials used to coat the surface of the cellulose sealing layer include sodium alginates, propylene glycol alginate, pectins, gellan gums, carageenans, xantham gum, locus bean gum, starches, soy protein , gluten and derivatives such as Arainoxylan ferulyate (AXF), zein, and gum arabic. These materials can be applied to the surface either before the film is made into capsules, or a as finishing treatment to pre made capsules. The selection of the preferred coating material is determined by the properties, contents and release characteristics required of the finished capsule. In order to provide flexibility these coating materials can be plasticised with agents such as glycerine or mono propylene glycol. A plasticiser to polymer ratio of 1:1 has been found to impart good flexibility for capsule manufacture. Where the agents are applied as a post treatment this plasticiser content can be significantly reduced.

A preferred aspect of the invention covers a soft capsule having a shell comprising three layers, namely a sealing layer, a barrier layer and a tie layer binding the two together.

The current preferred film comprises three layers, one or more of which are deformable by heat, providing between them the means for sealing and good oxygen barrier. These three layers function well over a wide range of individual thickness. The ratio is selected according the type of processing, capsule content, and capsule end application. In a typical oil bearing ingestible soft

capsule the carrier or sealing membrane is hydroxy propyl methyl cellulose plasticised with glycerine and propylene glycol or mono, di or tri acetin at a thickness of 10 to 150 microns, and the upper barrier layer is sodium alginate at a thickness of 5 to 50 microns plasticised with glycerine or sorbitol. In order to achieve a good level of adhesion between these layers a tie layer promoting adhesion consisting of propylene glycol alginate in the region of 0.5 to 20 microns is present.

It is preferred that the sealing layer is deformable by heat and seals using the established processes of heat, radio frequency or a combination of both. Alternatively, high frequency, ultrasonic or induction welding can be employed as the sealing method. Good results have been achieved using hydroxyl methyl propyl cellulose plasticised with glycerine and propylene glycol at 100 microns as a sealing layer with radio frequency as the sealing method.

To secure a barrier layer to the sealing layer sufficiently well that it will survive the rigours of the capsule forming process without delamination it has been found necessary and beneficial to use an adhesion promoter or tie layer. Propylene glycol alginate improves the adhesion of sodium alginate to hydroxy propyl methyl cellulose, as does a 50:50 blend of propylene glycol alginate and hydroxy propyl methyl cellulose. The materials used in this tie layer may also be plasticised with such materials as glycerine and or mono propylene glycol at around 20%. In this invention propylene glycol alginate has been found to perform this function well at a thickness of 4 microns.

The top layer provides the means to obtain specific barrier properties as well as time and site release such as area within the body in the case of ingestion. Time release can be controlled by thickness, but site release often needs formulation modifications. When sodium alginate or pectin is used as the barrier layer it can be made partially insoluble by introducing the surface to calcium ions thus forming a thin water insoluble layer which can be made to dissolve slowly in the presence of sequestering agents or when there is a change in pH.

In another aspect of this invention the film used for capsule formation is a 2:1 blend of hydroxy propyl methyl cellulose and propylene glycol alginate, plasticised with glycerine, propylene glycol or a combination of both at around 20-30%. In this aspect the film does not have discrete barrier and sealing layers, but the blend of the two materials produces a film which can be sealed and has different oxygen barrier properties to that of the hydroxypropyl cellulose layer in isolation. The thickness of the propylene glycol alginate/hydroxy propyl methyl cellulose blended film is determined by the casting process and chosen for specific capsule properties, but 200 microns has been found to work well.

The multi layered capsule shell film is prepared by coating the innermost sealing layer with an adhesion layer and a barrier or dissolution controlling layer. These coatings can be applied by, roller, Meyer bar, dipping, spraying, electrostatically, extrusion, sponge, gravure, flexo.

The preparation of the multi layered film can occur within the capsule manufacturing unit or off line whereby the finished multi layered film is supplied to a dedicated processing unit. It may also be formed by the application of the tie layer and barrier layer to capsules formed exclusively from the sealing layer. Where this application occurs off line as a post formed treatment by such methods as spray drying, dusting or coating, gum arabic, AXF, sugars, polyols and waxes have been found to work well.

The ability to seal any of the films described in this patent by heat inducing methods, including radio frequency, and the ability to produce strong finished seals can be enhanced by the application of certain materials, namely water soluble glycols, alcohols, lactones, acetins and pyrrolidones to the surface of the sealing layer. These materials also help to form a seal where the surface of the sealing layer is contaminated with oil. Propylene glycol, propanol, ethanol, butyrolactone, n- methyl pyrrolidone and gamma valerolactone have been found to work well in this case.

In one aspect the present invention provides a method of encapsulation characterised by supplying a novel multi layered film to a dedicated

encapsulation unit capable of deforming the film into two capsule halves, filling ,sealing and cutting.

In the encapsulation unit the film is pre formed preferably by the use of vacuum into capsule halves and the substance to be encapsulated is supplied between the films where it enters the two pre formed capsule halves during closing.

In a further aspect the pre forming process is enhanced by heating the forming head, or film to an elevated temperature of around 80-120C. In order to minimise the exposure of the capsule fill to high temperatures it is preferred that the film is heated just prior to capsule formation rather than the capsule forming head.

The encapsulation unit typically consists of a pair of flat forming heads or drums, where at least one of pair is formed with a plurality of indentations the size of the desired finished capsule on their face. Means for applying a vacuum to these forming heads is conveniently included, to help pull the film into the indentations and so assist in capsule formation. These heads are supplied by rolls of film which may be coated with several applications before reaching them. The pre formed capsules are filled while inside the forming heads before being sealed by the application of recognised and established methods, namely heat, radio frequency or a combination of these two. After sealing the capsules are cut out and ejected.

Whilst it is a preferred feature that the forming, filling, sealing and cutting occur at the same location it may also occur as a stepped process whereby the capsules are pre formed and filled at a different location to where they are sealed and where they are cut.

The invention also covers capsules formed in accordance with a method or by use of apparatus in accordance with the invention.

The invention will further be described, by way of illustrations.

Figure 1 is a schematic representation of a capsule formed from a single uncoated film. Figure 2 is a schematic representation of the preferred capsule shell. Figure 3 is a schematic illustration of a manufacturing units in accordance with this invention.

Detailed Description of the some of the Embodiments

Figure one illustrates an aspect of the invention, comprising a capsule with a shell wall consisting entirely of plasticised hydroxy propyl methyl cellulose, 1.

The capsule shell membrane illustrated in figure 2 comprises three layers. The sealing layer 1, is hydroxy propyl methyl cellulose plasticised with glycerine at 10% and propylene glycol at 18%, present at 100 microns. The top layer performing a barrier function 3, is sodium alginate plasticised with glycerine or sorbitol at 50 %, present at a thickness of 10 microns. In between these layers is a third layer 2, helping adhesion, namely propylene glycol alginate, present at a thickness of 4 microns. This intermediate layer may also contain a plasticiser up to 50% .

The three layer membrane is prepared by a series of two coatings from solution or by extrusion on to the surface of pre formed plasticised hydroxy propyl methyl cellulose film. The propylene glycol alginate is applied first followed by the plasticised sodium alginate. The coatings are applied separately by means of coating heads onto the surface of the hydroxy propyl methyl cellulose film on conventional coating apparatus. The three layer film can then be supplied to the encapsulation unit pre formed in rolls.

Figure 3 shows a capsule processing unit where the cutting process occurs remotely from the forming heads. The female forming head and cutting area are located in a cylinder, with flat faces exampled by 19, either side of the capsule forming areas exampled by 9. The female forming areas have raised side walls, 18, which help in the channelling of excess liquid fill away from the filling area. As the cutting does not take place at the point of capsule formation the female

forming unit is not sprung. Film passes over the forming head 6 and the forming cylinder 8. Vacuum is applied to draw the film into the forming heads. Forming head 6 has a forming cup 15 with a small groove cut in it, and has a grooved stripper plate assembly as in the previous embodiment. The filling injector 5 comes down and is then engulfed by the stripper plate groove 16 in the stripper plate 17. The filling injector 5 then withdraws as it fills the pre formed capsule. When the injector 5 has fully withdrawn, a further forward motion by forming head 6 causes a seal to be made as in the previous embodiment. This seal is completed by the action of heat, radio frequency or a combination of these two. When the capsule is made and filled the forming head 6 moves away from the forming drum 8 and the drum rotates to present another forming cup. The filled capsule which has not been cut remains held in place in the forming head 6 by means of vacuum. This capsule remains in the forming drum 6 until it is passed to cutting drum 7. This occurs by means of a loss in vacuum on the forming head 6, shown by the shaded area 15, and the presence of vacuum in the cutting drum 7. The formed capsule passes over the cutting head 10, where by means of a punch action it is cut free from the surrounding film. The finished capsule 12 remains in the cutting drum 7 until it drops into the tray 13 when vacuum on the forming drum 7 is release in the shaded area 16. The waste film 11 with holes in is transported via the rollers 14 to waste.

Example

Using the multilayer film as shown in figure 2 together with the apparatus described above good quality soft capsules were produced suitable for ingestion.

Claims

1. A soft capsule comprising a wall derived from a multilayer film consisting of three layers, namely plasticised hydroxy propyl methyl cellulose, proplyene glycol alginate and plasticised sodium alginate

2. A soft capsule comprising a wall made from a blend of plasticised hydroxy propyl methyl cellulose and proplyene glycol alginate.

3. A soft capsule with an innermost sealing layer made from hydroxy propyl methyl cellulose

4. Soft capsule made from a mulitlayered film which has superior oxygen barrier properties than hydroxy propyl methyl cellulose film of similar thickness.

5. A soft capsule film as in claims 1 to 3 capable of vacuum forming .

6. A soft capsule made using the film described in claims 1- 3 sealed by means of radio frequency

7. A soft capsule made using the film described in claims 1-3 sealed by means of radio frequency, ultrasonics or induction heat sealing.

8. A Soft capsule made using the film described in claims 1- 3 sealed by means of heat.

9. A soft capsule made using the film described in claims 1- 3 where the sealing process has been enhanced by the a surface application of an alcohol

10. A soft capsule made using the film described in claims 1- 3 where the sealing process has been enhanced by the a surface application of a glycol

11. A soft capsule made using the film described in claims 1- 3 where the sealing process has been enhanced by the a surface application of a lactone

12. A soft capsule made using the film described in claims 1- 3 where the sealing process has been enhanced by the a surface application of a pyrrolidone

13. A soft capsule made using the film described in claims 1- 3 where the sealing process has been enhanced by the a surface application of an acetin

14. A soft capsule containing an adhesion promotion layer containing propylene glycol alginate.

15. A soft capsule as in claim 10 where the material used is mono propylene glycol

16. A soft capsule made from a sealed layer of hydroxy propyl cellulose coated after formation with gum arabic.

Figure 1

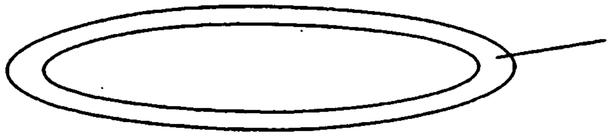


Figure 2

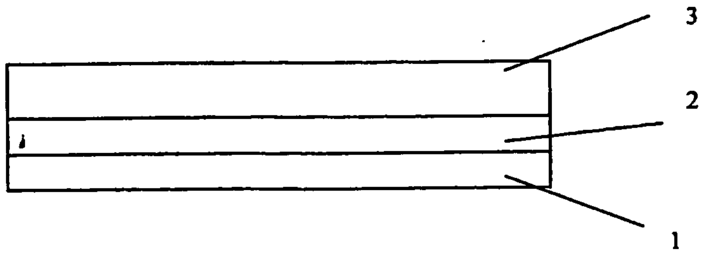
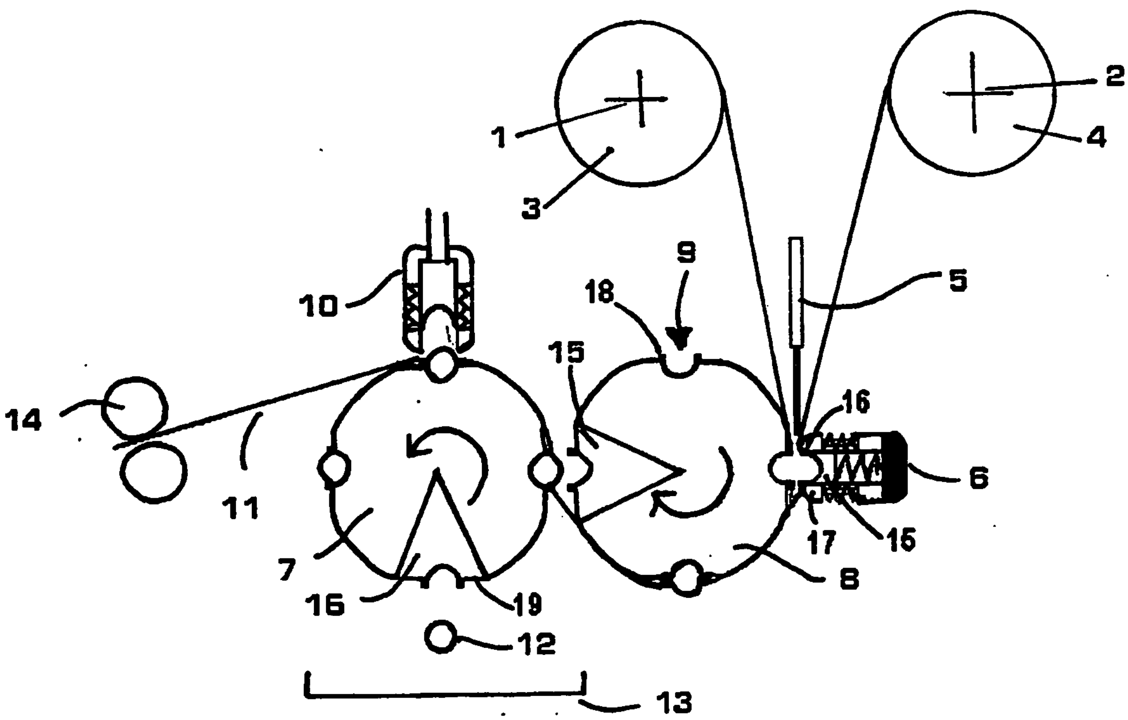


FIGURE 3



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03649

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 757 173 A (WARNER LAMBERT) 19 June 1998 (1998-06-19) the whole document page 2, line 28 - line 33 page 3, line 21 - line 26 ---	1-16
A	CHEMICAL ABSTRACTS, vol. 94, no. 2, 12 January 1981 (1981-01-12) Columbus, Ohio, US; abstract no. 7646q, R.-J. CHEN: "sodium alginate capsules for medical use" page 246; XP002130872 abstract & CHUNG TS' AO YAO, vol. 11, no. 1, 1980, pages 25-27, ---	1-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2000	01/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Benz, K

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9714 Derwent Publications Ltd., London, GB; AN 1997-149762 XP002130873 & JP 09 025228 A (EISAI CO LTD), 28 January 1997 (1997-01-28) abstract ---	1-16
A	US 4 501 759 A (GAJEWSKI) 26 February 1985 (1985-02-26) claim 1 -----	1-16

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2757173 A	19-06-1998	AU 5371498 A	15-07-1998
		EP 0946637 A	06-10-1999
		WO 9827151 A	25-06-1998
JP 9025228 A	28-01-1997	NONE	
US 4501759 A	26-02-1985	CA 1190084 A	09-07-1985
		US 4540587 A	10-09-1985